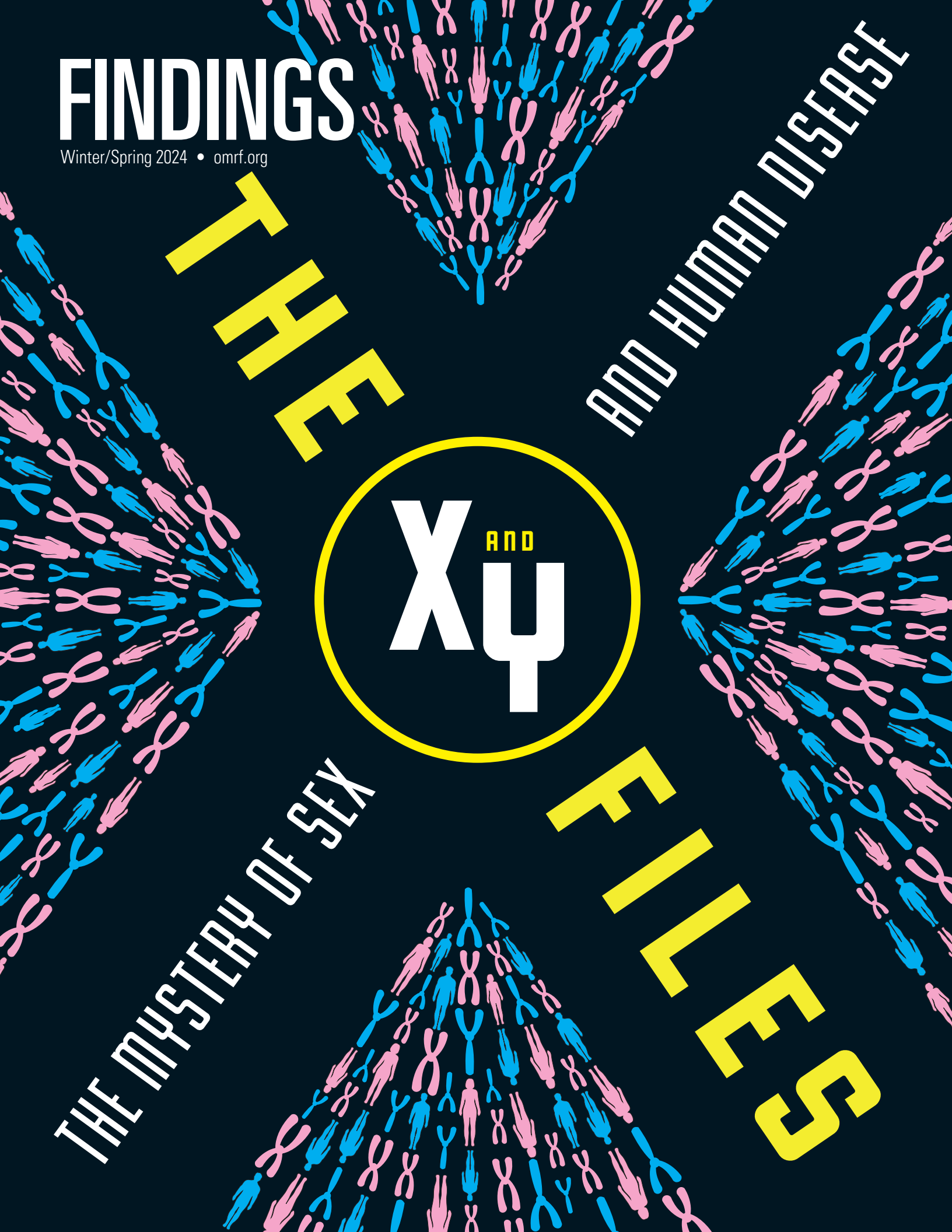
FINDINGS

Winter/Spring 2024 • omrf.org



FINDINGS

Winter/Spring 2024

FEATURE

THE X (AND Y) FILES

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In diseases ranging from Alzheimer's to influenza, OMRF scientists are trying to understand the role that sex plays.

ALSO IN THIS ISSUE

OMRF

Chartered in 1946, OMRF is an independent, nonprofit biomedical research institute dedicated to understanding and developing more effective treatments for human disease. Its scientists focus on such critical research areas as cancer, diseases of aging, lupus and cardiovascular disease.

405-271-6673 • findings@omrf.org

INSIDE FRONT COVER Jim Starr
ILLUSTRATION Elena Provik (5), Brad Gregg (6), Anna Heigh (8-9), Taylor Callery (23)
PHOTOGRAPHY Rob Ferguson (4, 14), Oklahoma Historical Society (4), Brett Deering (7, 8, 20), Charlie Neuenschwander (2, 9, 10, 17, 22)
BACK Courtesy of The Oklahoman

Road Music

Dr. Earl Mabry, here with his son Dr. James Mabry, played clarinet in a band of dentists and physicians that donated its proceeds to OMRF in the foundation's fledgling years.

WHEN I GET BEHIND THE WHEEL, I LIKE TO put on a little driving music. No matter the destination, I find a good soundtrack helps the miles roll by a bit more quickly.

And lately, I've had quite a few chances to learn new tunes.

In August 2023, we launched our 77 for 77 campaign. In honor of OMRF's 77th birthday, we're traveling to all 77 counties in Oklahoma over the next year. The idea is to thank all those who've supported us through the years and forge new bonds with folks who may not know about OMRF.

As of the week after Thanksgiving, which is when I'm writing this, we've made it to more than 20 counties. I'll share much more about my experiences in a future issue of Findings, but even though we have scores of communities yet to come, it's already been gratifying and tremendously fun to make so many connections and to learn about the ways OMRF has touched lives across the state.

Along the way, my wife, Amy, has been putting together an Oklahoma playlist. When we headed to Beckham County, she added "Wichita Lineman" and a few other Jimmy Webb songs. And because Roger Miller also grew up there, she included "King of the Road." (I mean, how could she not?)

But the melodies go beyond our van's stereo.

In Guymon, Dr. Martin Bautista was kind enough to host us, and he helped gather a big crowd of supporters and people interested in learning more about OMRF. We weren't surprised that Dr. Bautista is such a community influencer, as he's a talented and well-known gastroenterologist. What did surprise us was that he's also an America's-Got-Talent-worthy singer, and he showed it by opening the evening with a bang-up performance of Frank Sinatra's "My Way." Ol' Blue Eyes would've been proud.

Still, my favorite musical moment came from Dr. Earl Mabry. We met Dr. Mabry in Enid, where he established his dental practice on the heels of World War II.

Dr. Mabry had served as a dentist in the U.S. Navy, and he'd also go on to do so in stints with the Army and Air Force. Between military assignments, he cared for patients in northwestern Oklahoma and raised a family that would grow to include nine children.

You'd think this would have been more than enough to fill his days and nights. But Dr. Mabry didn't feel life was complete without music.

Growing up in Altus, he played the saxophone and clarinet in a traveling orchestra that took shape in, of all places, a local barbershop. They performed jazz and big-band pieces throughout the western part of the state, booking for "whoever wanted a 10-piece orchestra," he says. The money "wasn't great," but for a high-school kid, "it was more than working at an ice cream shop."

When he settled in Enid, Dr. Mabry met several other medical professionals who also played instruments. They began getting together to practice jazz standards in one physician's basement, and when word got out in the medical community, the "Doctors' Band" started booking gigs.

As dentists and physicians, they were accustomed to getting paid for their services, and this was no different, says Dr. Mabry. "The first time someone invited us to play for them, we gave them a price and took their money." However, each time the band got paid, they donated it all to OMRF.

Dr. Mabry doesn't recall why, exactly, he and his bandmates chose OMRF as their charitable beneficiary. But his son, Dr. James Mabry (like his dad, an Enid dentist), believes it stemmed from OMRF's founding campaign: In the late 1940s, health professionals around the state raised funds to build a new medical research foundation.

The ensemble stayed together for more than half a decade, then disbanded around the time the elder Dr. Mabry was called back into military service. After he returned home, he channeled all of his musical energy into the organ, an instrument he played into his 80s.

Dr. Mabry turns 104 this January. During our visit, I learned that in all this time, he's never been to OMRF. So, of course, I invited him, along with his wife, Carol, and his son. I wanted this jazz-loving donor and his family to see the place the Doctors' Band had helped create.

When they accepted, it was music to my ears.

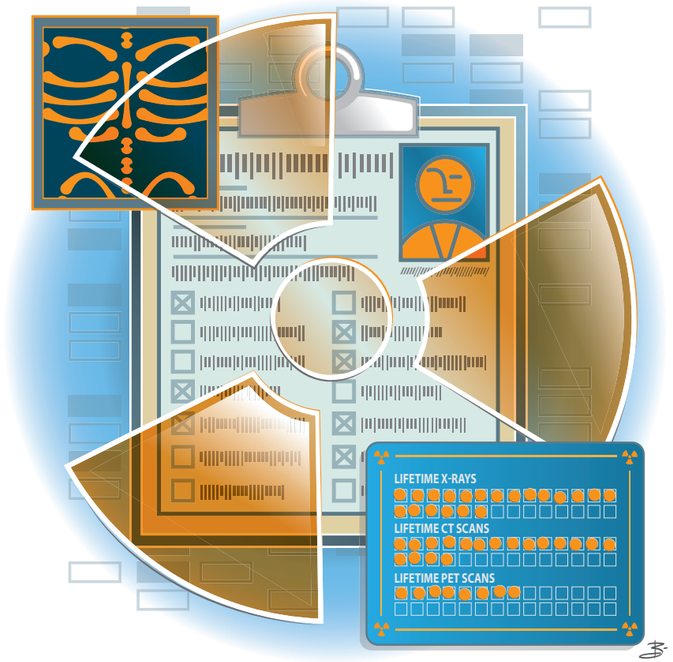
Andrew S. Weyrich

"It's incredible to have a resource in our state with world-class researchers and doctors. They provide the kind of care Oklahomans often think they need to travel out of state to get."

Meg Salyer

Meg Salyer has served as a community representative on OMRF's conflict of interest committee for more than a decade. When a member of her family began experiencing autoimmune disease symptoms, she knew exactly where to turn: OMRF's Rheumatology Center of Excellence. The real estate developer, who also recently joined OMRF's Board of Directors, says "Having a jewel like OMRF in our community provides a lot of comfort."

Radiation Risks?



Dear Dr. James,

I've had exposure to X-rays, MRIs and CT scans over my life. I understand the effects of radiation from these scans are cumulative, but nothing in my medical records tracks this. Shouldn't it?

Paul Thomson
Edmond, Oklahoma

Dr. James Prescribes

When it comes to radiation exposure from medical imaging, most people's top concern is cancer. Radiation can, indeed, increase cancer risk. But the good news is that routine X-rays – like those we get at the dentist or for a fractured bone or respiratory issue – expose adults to very low radiation levels. And MRIs, which use a large magnet and radio waves, use no radiation at all.

Still, many experts are concerned about tests with higher doses of radiation, such as CT scans and nuclear imaging tests like PET scans. Proponents of tracking these tests in medical records argue it can help providers make more informed decisions about the necessity of future imaging procedures, especially in cases where non-radiation-based methods, like ultrasound or MRI, could suffice.

There are challenges to implementing such tracking. There's no universally accepted method for quantifying and recording radiation dose. Total exposure varies based on factors that include the type of test, the device (newer ones generally use less radiation), the duration of the scan, and a person's size, age, and sex. Patients also receive imaging at different healthcare facilities and during dental visits, which would further complicate efforts to create a universal tracking system.

Even if we developed a universally agreed-upon way to tally radiation exposure from imaging, the amount of radiation that might increase a person's cancer risk remains an open question. Most research on this topic has looked at people exposed to high doses of radiation, such as atomic bomb survivors and uranium miners. The risk from low-level radiation exposure isn't easy to calculate from these studies.

When a physician prescribes medical imaging that involves radiation exposure, such as a CT scan or nuclear medicine testing, it often represents the best way to look for cancer or other diseases. In these situations, the potential benefit of these tests usually outweighs the risks. Still, any patient concerned about radiation from one of these tests can ask their provider if there's an alternative, such as a lower-dose X-ray or a test without radiation, and whether they can shield the parts of their body that aren't being imaged.

Unless you received high doses of radiation during cancer treatment as a child, based on what we know today, any increase in your risk for cancer due to medical radiation appears to be slight. While healthcare systems may not track cumulative exposure, you can maintain your own records of imaging procedures, especially if you frequently require them. This can help decrease duplicate testing. And if you wish to ask your healthcare provider about the issue, having a log will facilitate a more informed discussion.

Dr. Judith James, who was recently inducted into the National Academy of Medicine and the Oklahoma Hall of Fame, is OMRF's executive vice president and chief medical officer. Submit your health questions at omrf.org/AskDrJames.

Living Legacy

An OMRF donor follows in the footsteps of his mentor

From a rocking chair on the porch overlooking the rolling hills of his eastern Oklahoma ranch, Kenneth Steele sums up his career in a breath: "I was a cowboy."

In 1959, married with three young daughters, Steele needed work that was more stable than his gig in the oil field. The then-23-year-old found it on the 10,000-acre Chapman Ranch in Holdenville, Oklahoma.

The job in his native Hughes County paid less than the $1.65 an hour he pulled in as a roughneck, but it included a furnished home, space for a vegetable garden, and a side or two of beef a year. It also set him on a path toward a life of generosity, thanks to the guidance of the ranch's owner.

"After about a year working there, Mr. Chapman took an interest in me and taught me his way of doing things," says Steele. Mr. Chapman was James A. Chapman, a legendary Oklahoma oilman and rancher. With his wife, Leta, Chapman set up a trio of trusts benefitting OMRF. The pair first named the foundation as a beneficiary of a charitable trust in 1949, the year OMRF began construction.

In the seven-plus decades since, funds from the Chapman Trusts have bolstered OMRF in good times and bad, provided start-up dollars to recruit new scientists, and supported countless renovation and construction projects. The trusts also help fund administrative costs at the foundation, enabling donations from others to go directly to research.

Under Chapman's mentorship, Steele learned that nothing ever went to waste. More than once, Steele watched Chapman hammer bent horseshoe nails so they could be reused. If a building needed to be taken down on his property, says Steele, "he saved everything – all the lumber, even the nails."

"Mr. Chapman was a self-reliant, independent kind of man, but he wanted to take care of people in need," says Jeff Sanders of Bank of Oklahoma, which serves as a trustee of the Chapman Trusts. "He also wanted to invest in basic science to improve lives far in the future, which is what drew him to OMRF."

"The Chapman way" has guided Kenneth Steele in life and philanthropy.

Kenneth and Bernice Steele have given to OMRF for 20 years and counting.

Steele lived on the Chapman family's Holdenville ranch working cattle for 31 years. He also moonlit at other Chapman properties that dotted the state. "I'd go to the ranches in Roff and Davis and learn from the cowboys there, who learned from Mr. Chapman," Steele says.

James Chapman passed away in 1966, and Leta Chapman in 1974. By then, Steele had risen to lead the Holdenville ranch, which continued operations after both Chapmans' deaths. Steele retired from the Chapman enterprise when the Holdenville land was sold in 1990, shifting his focus to his own ranch 3 miles down the road, which he still runs "the Chapman way" at the age of 87.

When Steele and his wife, Bernice, found they had the means to give back, the decision to support OMRF was easy. "I wanted to pattern all I could after the Chapmans," he says. "They gave a portion of what they had to OMRF, and I thought if they did that, it'd be alright for me to do it, too." The Steeles' streak of consecutive years of donations to OMRF now stands at 20.

Today, Steele continues to show his family how he learned to live and leaves the rest up to them. "I don't suppose I'm the kind to tell others what to do," he says, "but when I read what OMRF is doing, I feel proud to have a small part in it."

PLANTING SEEDS

THE PRESBYTERIAN HEALTH FOUNDATION NURTURES OKLAHOMA'S BIOMEDICAL RESEARCH PROGRESS

Rick McCune, left, and Tom Gray are devoted to maintaining Oklahoma as a center of research excellence.

Tom Gray and Rick McCune aren't scientists. But as chairman of the board and president, respectively, of Oklahoma City's Presbyterian Health Foundation, the pair shares a goal with OMRF's researchers: to improve the health of all Oklahomans.

PHF was founded in 1985 following the sale of Oklahoma City's Presbyterian Hospital, then the largest hospital in the state. With the invested proceeds from that original transaction and, later, the sale of the PHF University Research Park, the foundation has awarded more than $215 million to Oklahoma organizations aligned with the foundation's mission.

While there are several hundred entities like PHF, as far as Gray and McCune know, the foundation is unique among them in dedicating the lion's share of its budget to one thing: accelerating biomedical research. And every one of those dollars is awarded to research institutions on Oklahoma City's Health Center campus.

"We want to keep growing Oklahoma as a center of research excellence," says Gray. "You do that through disciplined investments and funding."

Throughout the year, the foundation gives grants that support needs and programs at OMRF and the University of Oklahoma Health Sciences Center. Those awards include seed funding for new ideas, an M.D./Ph.D. training program, equipment, scientist recruitment and retention, and collaborative grants, which enables teams to work across disciplines.

Along with Gray and McCune, a staff of three oversees day-to-day administration and finances. The team relies on PHF's scientific advisory committee, made up of experienced local researchers, to evaluate grant applications and make funding recommendations to its 13-member board of directors.

At OMRF, two of the most utilized awards are for equipment and seed funding, says Vice President of Research Dr. Courtney Griffin.

Unlike seed grants that support one or two labs, equipment grants can benefit an entire research program. And while funding for high-powered microscopes and refrigerator-sized DNA sequencers may not grab many headlines, there's a domino effect.

"You have to have great researchers to produce groundbreaking research," McCune says. "To attract and retain great researchers, you have to have cutting-edge scientific equipment."

Seed grants, on the other hand, fund proof-of-concept experiments or allow a scientist to develop a technology they need for a particular project. "That can be the difference between getting federal funding and not," Griffin says. And she would know. When the National Institutes of Health awarded her a seven-year grant in 2019, it was thanks in part to PHF seed funding for developing two new research models. Without those models in hand, Griffin says, "almost no grant reviewer is going to be satisfied."

Presbyterian Health Foundation's team is led by McCune and Gray and also includes, back row from left, Jodi Coats, April Stuart and Beverly Self.

In 2022, the NIH received more than 36,000 applications for its oldest and most commonly awarded grant mechanism and others equivalent to it, the R01. These multimillion-dollar grants provide several years of support for a scientist's independent research program. Of those tens of thousands of applications, the NIH ultimately funds only a small fraction.

With the fierce competition for federal dollars, scientists need to demonstrate their ideas have a high likelihood of success to have the best shot at funding, says Griffin. "There just isn't enough money to go around," she says. "So, if the NIH is going to invest millions of taxpayer dollars in a scientist, they tend to tip the scales toward someone with a better chance of breakthroughs."

OMRF scientists have a strong track record of winning this kind of funding. Currently, the foundation's researchers have more than 50 active R01 or equivalent grants. Through its seed funding, PHF has played a role in securing scores of them, aiding in bringing tens of millions of federal dollars into Oklahoma. In 2023, the NIH awarded one of those grants to OMRF cell biologist Dr. Susannah Rankin.

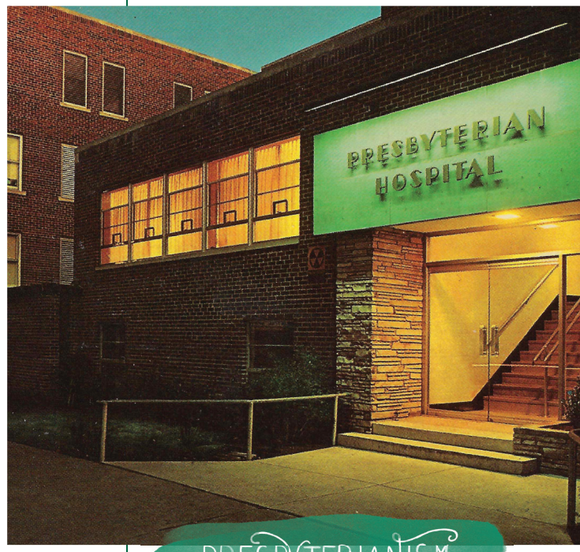
Rankin studies how our cells package chromosomes during cell division. When errors occur in the process, they can lead to issues ranging from miscarriages, genetic disorders, and birth defects to cancer. By understanding everything that must happen for cell division to go right, scientists can help prevent mistakes from happening in the first place.

In her application to the NIH, Rankin used preliminary data she'd generated through multiple PHF seed grants. "That kind of help to do those early steps – it can just change things," she says. "It's incredibly hard to get federal funding without early-stage results." To her, PHF's willingness to gamble on early-stage projects "is forward-thinking. Without high-risk, high-reward research, nothing would happen."

For its part, PHF doesn't fear projects that ultimately fall short of their goals, says April Stuart, PHF's director of grants and programs. "Failure closes a door. If an experiment tells someone else where *not* to look, we see that as its own success."

Dr. Susannah Rankin

No matter the outcome, Gray says the potential payoff for Oklahomans and people everywhere is worth betting on. "When you plant a seed, either it's going to produce, or it's not." But without seeds, he says, one thing is assured: Nothing will grow.



PRESBYTERIANISM & HEALTHCARE

In Oklahoma City, there was only one Presbyterian Hospital. But it was part of a long tradition of hospitals in major metropolitan areas – Charlotte, Dallas, Denver, Philadelphia and Pittsburgh, to name a few – that bore the "Presbyterian" moniker. Although the hospitals were not formally affiliated, like many healthcare facilities, they all started as sectarian institutions. And as their names suggest, each of them had a mission that was in some way tied to that particular branch of Protestantism.

For example, at New York's Presbyterian Hospital, in addition to medical care, Harper's Weekly in 1872 wrote that patients received "the ministrations of the Gospel agreeably to the doctrine and form of the Presbyterian Church." Although the hospital doors were open to all, The New York Times reported that many patients claimed to be Presbyterians – just in case.

Pain Killer

Dr. Matlock Jeffries is exploring novel ways to bring relief to people with arthritis

For his osteoarthritis research, Dr. Matlock Jeffries relies on patient volunteers like Roberta Roush.

Just about everybody knows – or is – someone with osteoarthritis. An estimated 32 million Americans live with OA, including more than half of those over 65.

"It's the most common cause of disability in the U.S.," says OMRF's Dr. Matlock Jeffries, a board-certified rheumatologist who has studied the condition for more than a decade. Yet, he says, "We don't currently have any osteoarthritis-targeted drugs."

Osteoarthritis stems from the loss of cartilage between bones and joints. The knee is the most frequently affected, and the only definitive treatment, joint replacement, is the leading expense for Medicare each year. In total, the National Institutes of Health estimates that the condition levies an annual economic burden of more than $130 billion on the nation's economy.

Despite its toll, there's no treatment to slow, stop or reverse OA, and doctors can't predict its development or progression. Jeffries wants to change that.

During medical school at the University of Oklahoma Health Sciences Center, he worked as a research technician in an OMRF lab focused on lupus epigenetics, or how external factors can cause changes in how genes work. It set Jeffries on a path to specialize in internal medicine and rheumatology, where he imagined he would study and treat autoimmune conditions that affect the joints, muscles and ligaments.

Early in his residency, the physician-scientist realized that his patients "all had OA." When he dug into the medical literature, he found little research on the condition. "With how common it was, I thought that was strange. I wondered if we could do what we were doing with lupus and look at the epigenetics of OA," he says.

The question gave birth to the dual focus of Jeffries' career. Today, he treats patients with OA in OMRF's Rheumatology Center of Excellence. In his lab, he studies both the epigenetics of the disease and how it is linked to changes in our microbiome, the trillions of tiny organisms that live throughout our bodies. He does it using a unique strain of mouse called a "superhealer." These rodents naturally (and unusually) heal wounds to their ear cartilage, which resembles knee cartilage.

Jeffries transplanted microbes taken from the gastrointestinal systems of the superhealer mice into a group of mice with average healing capabilities. After the transplant, the non-healer mice were protected from developing OA, as were their offspring. The results, which Jeffries says were "completely unexpected," indicate the gut microbiome has more influence on the body's immune response to injury than previously understood.

To guide their next steps, his lab is now working to understand whether certain bacteria lead to that ability to heal or if it's linked to an overall change in the microbiome after an injury. Time will tell whether a whole microbiome transplant or simply a strong probiotic cocktail could yield the same results in humans.

> **"We don't currently have any osteoarthritis-targeted drugs."**

Still, Jeffries says this particular path shows potential for the treatment of post-traumatic OA, which develops following an injury to a joint like a ligament tear. This form of the disease accounts for an estimated 3 million OA cases and is one of the top reasons for injury-related discharge among active-duty U.S. soldiers. "Potentially, if an injury was caught early enough, we could change someone's outcome," he says.

•••

For Jeffries and others seeking to develop new treatments for OA, clinical trials represent a major obstacle.

Researchers conduct clinical trials over a relatively short period of time, with even the longest phases typically spanning no more than a year or two. During this time, they're able to observe the benefits (or not) that come from a new form of treatment.

However, in osteoarthritis, this timeline would be stretched substantially. Disease progression can occur over a span of decades, and, says Jeffries, "It's really not feasible for a clinical trial to last 10 years for Phase I, 10 years for Phase II, and have it take 40 or 50 years for a new drug to come to market."

For effective OA trials, he says, "What we really need is the ability to identify patients who are likely to experience rapid disease progression." In 2022, his research team published a study of knee and hip OA showing they could find these patients with a single blood draw.

OMRF has filed a patent on the technology and is currently seeking an industry partner to develop it. The hope, Jeffries says, is that the discovery will enable the completion of clinical trials for OA treatments in the span "of a few years instead of a few decades."

Meanwhile, in the ongoing search for new therapeutics for the condition, research volunteers represent another critical piece of the puzzle. "Patients who are willing to donate samples are the only way forward," Jeffries says. "We can't make progress without them."

To continue his work, Jeffries relies on patient volunteers like Oklahoma City's Roberta Roush. Roush's doctor diagnosed her with knee OA in 2021 at age 59. She still runs an average of 20 miles a week, but after watching her father undergo two OA-related knee replacements, she wanted to do her part to advance research on the condition.

When she saw an ad for one of Jeffries' OA studies, Roush called right away to see if she qualified. "They made it so simple," she says. "It was a no-brainer to get involved."

Roush visits OMRF every six months to give blood, saliva, and microbiome (stool) samples, and take a single X-ray. All in, she guesses the process takes about an hour twice a year. And even though OMRF compensates her for her time and effort, Roush prefers to donate the money back to the foundation. "It's an honor to participate," she says. "I'm just happy to help."

You Can Help Make Arthritis History

Volunteers with and without osteoarthritis are needed to advance research on the condition. For information on joining OMRF's OA studies, visit omrf.org/oa, call 405-271-7745 or email clinic@omrf.org.

THE X and Y FILES

By Adam Cohen

In diseases ranging from Alzheimer's to influenza, OMRF scientists are trying to understand the role that sex plays.

Research by Dr. Michael Stout suggests that a female sex hormone may be helpful in reversing metabolic problems in males.

As a postdoctoral researcher at the Mayo Clinic in Minnesota, Dr. Michael Stout had his share of disagreements with his mentor.

The senior scientist, an esteemed researcher in the field of aging, had recently turned the focus of his laboratory to the deterioration cells undergo as they grow older. Stout's job was to find ways to trigger this decline. However, despite his best efforts, he was failing. Or at least that's what he thought.

Whenever Stout showed the results of his work, his mentor took issue. The young scientist had repeatedly proven unable to achieve the desired outcome, and his mentor contended that the fault lay not in the compound Stout had been using – a form of the female sex hormone estrogen – but, rather, in the design of his trainee's experiments.

So, Stout set out to settle the matter once and for all.

He incorporated the compound, known technically as 17 alpha-estradiol, into a special diet. Then he fed it to 18-month-old mice and studied what happened.

Again, he found no evidence of cellular deterioration. But this time, he also saw a series of biological results that suggested almost the opposite effect.

With the estrogen supplement, the mice showed improved insulin sensitivity, a key predictor of diabetes and other metabolic illnesses. "They also had reduced fatty liver disease, reduced DNA damage and reduced body fat," Stout says. By many measures, the animals had undergone a surprising "metabolic transformation."

The animals' body clocks seemed to have rewound, and their systems for processing food and generating energy no longer resembled those of rodents in late middle age. "They looked like 6-month-old mice," says Stout.

Just as interestingly, the mice – all males – showed no sign the female sex hormone was causing the growth of breast tissue, reduced sperm production, loss of libido, redistribution of body fat, or loss of muscle mass. "So," says Stout, "it appeared you could take an estrogen and get all of these metabolic benefits without feminizing effects."

When Stout reran the experiment with female mice, though, he got very different results. Only in extremely obese animals did he see any metabolic improvement, and those changes were mild.

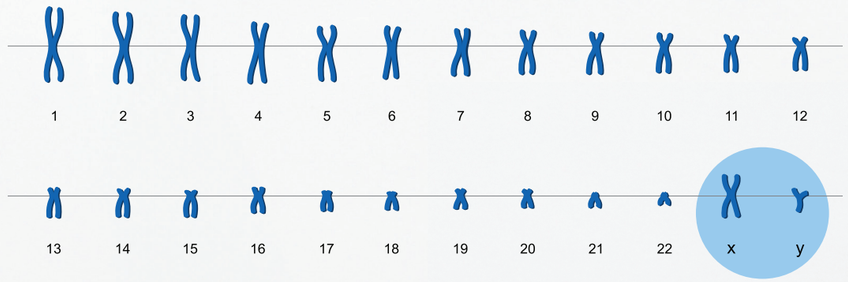
At first blush, the disparity appears puzzling. After all, you might presume that giving a female sex hormone to older females, whose bodies produce less of it as they age, would be beneficial. You might also ask why giving that same sex hormone to males would reverse numerous biological processes linked to advancing age.

Yet these results mirrored other experiments with the compound. When researchers fed mice a diet supplemented by 17 alpha-estradiol, males lived 20% longer. Meanwhile, it had no impact on females' lifespans.

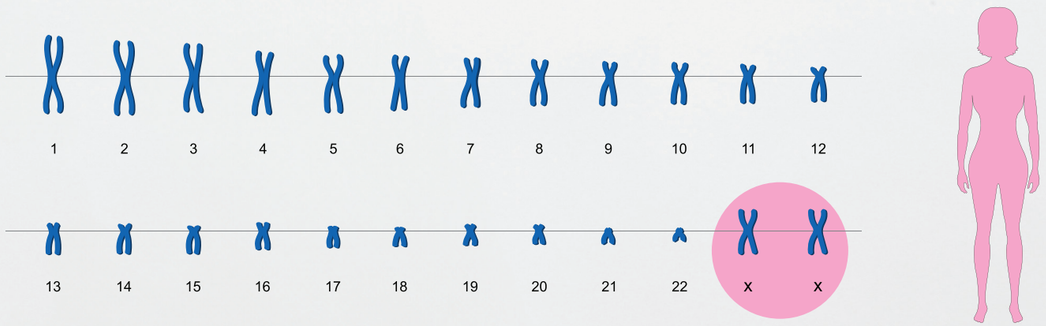
For Stout, who joined OMRF in 2021 as an associate professor, the work has formed a foundation for his studies going forward. "Our lab's overarching goal is to figure out if there's a role for sex hormones, and the receptors in the body

Sex Education

Men and women are each typically born with 23 pairs of chromosomes. Twenty-two of those are identical in males and females, but the final pair differentiates the two sexes: Females have two X chromosomes, while males have an X and a Y.



The genetic codes stored on these thread-like structures are wrapped in the nucleus of each of our cells, and the information contained on that 23rd pair of chromosomes helps drive the development of sex organs – testicles in men, ovaries in women. These organs, in turn, produce the lion's share of hormones that are instrumental in sexuality and fertility. For women, the primary sex hormones are estrogen and progesterone; for men, it's testosterone.



Scientists at OMRF are now examining the roles sex chromosomes and hormones may play in illnesses ranging from Alzheimer's to respiratory diseases.

that interact with them, in affecting disease burden in a sex-specific way."

The idea that diseases could strike men and women differently might seem obvious. But until recently, that concept was anything but.

A Population Ignored

The 20th century marked a watershed for medical research, with a depth and breadth of discoveries and breakthroughs – antibiotics, vaccines, therapies for illnesses ranging from cancer to cardiovascular disease – that dwarfed all that had come before. Yet the medical knowledge gathered during this time came almost exclusively from men.

For example, the National Institutes of Health launched its pioneering Baltimore Longitudinal Study of Aging in 1958 with the ambitious goal of exploring how the passage of time affects all systems in the body. However, it took another 20 years (and 1,000 research subjects) before the project enrolled its first woman.

In the 1980s, researchers at Harvard Medical School and Brigham and Women's Hospital created the Physicians' Health Study to examine the risks and benefits of regularly taking aspirin and various vitamin supplements. When the landmark project wrapped up, concluding that low-dose aspirin decreased the chances of a first heart attack, scientists had followed more than 22,000 research volunteers. None of them were women.

At times, the tilt toward men took research down absurd paths. After doctors observed that women tend to have lower rates of heart disease before menopause, researchers conducted the first trial of whether hormone supplementation might have a protective effect for coronary disease. The study enrolled 8,641 men and no women. Another NIH-supported project looked at how obesity affected breast and uterine cancer; again, head-scratchingly, it included only men.

As more women entered the field of research, they began to call attention to the disparity, and the NIH stepped up efforts to balance the scales. But when progress proved halting, lawmakers stepped in. "Somehow," one representative noted during congressional hearings, "I find it hard to believe that the male-dominated medical community would tolerate a study of prostate cancer that used only women as research subjects." In 1993, Congress mandated that all federally funded clinical research studies include women.

Still, the sex gap persisted in laboratory research, where scientists perform pre-clinical experiments involving cells and laboratory animals. Accounting for sex in these types of studies can be biologically difficult, requiring a level of specialized analysis many laboratories lack. And generating

Sex Discrimination

"For a long time, people thought that once they understood diseases in males, they could just transfer that to females and it would be the same."

Dr. Sarah Ocañas

statistically reliable results for each sex drives up the time, effort and expense of experimentation, as the studies must involve a larger number of samples or subjects.

In 2016, the NIH also sought to level this playing field, enacting a policy calling for the inclusion of both sexes in studies involving cells and animals. As the largest funder of nonprofit and academic research in the world, that call appeared to make an immediate impact: A report analyzing 34 biology journals found that within a few years of the policy's adoption, the number of pre-clinical studies that included both males and females had almost doubled.

But while the numbers looked promising on their face, a deeper analysis revealed a more nuanced picture. Specifically, while many studies reported sex differences, most failed to dig deeper in an effort to root out a biological explanation.

In neuroscience, for example, studies showed a spike in the inclusion of both males and females. However, fewer than half even broke down the results by sex. "If we're not doing sex-based analysis," the report's co-author told the journal Nature, "we're essentially leaving half the data on the table."

Women, Men and Alzheimer's

Dr. Sarah Ocañas became interested in neuroscience as "a little kid," thanks to an encounter with a female neurosurgeon. "I was very inspired by her as a woman in a male-dominated field," says Ocañas, who grew up in a small town in upstate New York.

Ocañas double-majored in mathematics and biology as an undergraduate, then joined Teach for America, a nonprofit that sends educators to underserved communities. For seven years, she taught high school calculus, statistics and anatomy in Texas' Rio Grande Valley. "Teaching was rewarding, and I enjoyed it, but it wasn't something I could see myself doing in the long term," she says.

While in Texas, she also earned a master's degree in mathematics, and one of her projects involved modeling the electrical activity of neurons. It sparked something in her. "I wanted to figure out how I could use math to solve neuroscience problems," she says.

In 2017, she enrolled in the graduate program in neuroscience at the University of Oklahoma Health Sciences Center. It was, she says, "a very exciting time to come back to science." Technology had improved by leaps and bounds, and data that had once taken years – and cost millions – to gather could be generated in 24 hours for a few hundred dollars. "The capabilities we had just exploded," she says.

With the help of these new methods, her mentor, OMRF's Dr. Bill Freeman, had detected higher levels of inflammation in the brains of healthy, older female mice than in their male counterparts. "We wanted to know what was responsible for this," says Ocañas. For her Ph.D. dissertation, she performed a series of experiments, then used a variety of sophisticated analytical approaches to identify the culprit: microglia, a type of resident immune cell in the brain.

The work earned Ocañas a 2022 NIH Director's Early Independence Award, the first ever given in Oklahoma and one of only 14 nationwide. Totaling $2.2 million over four years, the grant enabled her to bypass the traditional postdoctoral fellowship and open an independent research lab at OMRF, where she set out to answer a new – but related – set of questions. All of them center on one of medicine's most intractable and devastating conditions: Alzheimer's disease.

In America, there are nearly twice as many women as men living with Alzheimer's. That's partly due to the fact that there are more older women than men, and the older you are, the greater your chances of being struck by the neurodegenerative illness. But that's not the whole story.

Studies have shown that among older women and men of the same age, women are more likely to develop Alzheimer's. In addition, says Ocañas, women have more profound biological manifestations of the disease. "The primary hallmarks of Alzheimer's within the brain are the accumulation of plaques and tangles, and women tend to have worse plaque buildup," she says. "They also have worse cognitive decline." However, she says, if men get the disease, they tend to die more quickly. "It appears that even though women experience the disease in a more aggressive way, they may also have some sort of resilience in terms of surviving."

Ocañas is now studying the role sex chromosomes may play in the differing ways Alzheimer's strikes women and men. From a genetic perspective, she says, it makes perfect sense that we'd see disparities.

Of humans' 46 chromosomes, males and females have 45 in common. However, each sex carries a different final chromosome, depending on whether we are female (X) or male (Y). That means the two sexes share a bit less than 98% of the genome.

Meanwhile, says Ocañas, "We are almost 99% genetically identical to chimpanzees of the same sex." Forget about women being from Venus and men from Mars. To see the magnitude of the genetic gap between sexes, we need only visit the nearest zoo: "Men and women have more in common with chimps of the same sex than we do with one another."

To understand sex's part in Alzheimer's, Ocañas is now looking more deeply at the ways in which the chromosomes vary between males and females. "We want to know how those could be contributing to the differences we see in the brain," she says. Specifically, she's examining how they may cause microglia, the resident immune cells, to become activated, a process that appears linked to the cognitive decline that comes with Alzheimer's.

With a new grant from the Alzheimer's Association, she's also investigating how the steep decline in sex hormones as women age may impact Alzheimer's. "Menopause," she says, "has historically been neglected in studies." Her lab will probe whether the loss of estrogen that accompanies menopause could be a driver behind Alzheimer's higher incidence and disease burden in women.

In the longer term, she aims to explore whether she can identify certain groups of women for whom hormone replacement therapy might help prevent or treat Alzheimer's. "If we're going to find an effective intervention, it's not going to be one-size-fits-all," she says. "It's going to have to be a more personalized approach where we're taking into account sex, hormone status and genetics."

Dr. Susan Kovats has found that sex hormones can impact the body's immune responses.

Today, when a woman sees a doctor, that physician likely will have learned using models of disease developed primarily by studying men. One of Ocañas' ultimate goals is to help correct that imbalance. "If clinicians are trained on the biological sex differences in disease," she says, "then they can provide equitable healthcare to men and women."

The Weaker Sex?

The immune system is one of those areas where men and women are not created equal. A complex network of biological systems that includes the bone marrow, skin, spleen and thymus, it protects the body from viruses and bacteria. But when the body is called to fight off outside invaders, men are the weaker sex. For many years, though, medical researchers believed the opposite.

In studies of influenza, they observed that women consistently experienced more severe symptoms than men. For that reason, scientists concluded that female immune systems must lag their male counterparts.

Then came Covid-19. As with so many aspects of science, the virus caused researchers to rethink their ideas about sex differences and immune response.

Once again, they saw that women often fared worse in the early phases of infection. But, says OMRF immunologist Dr. Susan Kovats, scientists realized that rather than highlighting a weakness, the pronounced symptoms signaled a more robust immune response.

"If you feel crappy, it's not because you're failing to get rid of the virus. It's because your immune response is really strong," says Kovats. When researchers went back and reexamined their studies of flu, they found the same thing. What's more, they determined that the worst symptoms appeared in women in their reproductive years.

To Kovats, who studies how sex-related hormones impact immune responses, this made sense. "During reproductive years, women have a lot of estrogen," she says. She hypothesizes that the female sex hormone may fuel women's more vigorous immune responses. It could also help explain why female immune systems seem to respond more effectively to Covid vaccines – and why, with the loss of estrogen, the virus becomes more dangerous as women age.

However, the increasing severity of Covid and other respiratory viruses as we grow older is not limited to women. Again, says Kovats, that's unsurprising, as men also experience a drop-off in male sex hormones like testosterone as they grow older. While that decline follows a more gradual curve than the sudden hormonal cliff women experience with menopause, the end result is the same: a loss of protection and other benefits sex hormones offer.

Because men's immune systems start at a disadvantage, says Kovats, they also end at one when they reach their

70s, 80s and beyond. “Because of the loss of testosterone, along with the natural reduction of the ability to produce interferon” – a protein that inhibits virus replication – “elderly men do the worst” with Covid and other respiratory infections like it.

In her lab, Kovats and her research team are studying how estrogen affects immune cells and changes the way they function. “If we know how women and men respond differently, then we might be able to figure out therapeutic approaches that allow us to manipulate different immune pathways,” she says. Like her colleague Ocañas, she sees sex differences as a key to unlocking the effectiveness of treatments, both existing and new. “If men and women have different immune pathways when they are sick or they get an infection, can we find different treatments that target those pathways?”

Similarly, decades spent parsing the relationship between sex and the immune system have convinced Kovats that, while greater inclusion of women in studies has improved our knowledge base, current approaches to research often continue to ignore crucial information. “Whenever we take blood, we need to be measuring hormone levels,” she says. “We need to be asking women if they’ve undergone menopause, if they’re on hormone replacement therapy. Do they have ovaries?”

Without this information, she says, the data paint only part of the picture. And any conclusions drawn from that data will likewise remain incomplete.

Hiding in Plain Sight

At least for one disease area, that incomplete picture has been hiding in plain sight for years. “We’ve known for some time that most autoimmune diseases are heavily female,” says OMRF’s Dr. Hal Scofield, a physician-scientist who has studied the conditions for more than three decades.

In diseases that have an outsized effect on one sex, “Some of that has got to be biologic,” says Dr. Hal Scofield.

In autoimmune disease, the body mistakenly turns its defenses against itself. Encompassing more than 80 known conditions, autoimmune diseases affect an estimated 25 million Americans, about 20 million of whom are women. For individual autoimmune illnesses, the statistics can be even more unbalanced: Lupus strikes women at a rate of about 9 to 1; in Sjögren’s disease, where the body destroys its moisture-producing glands, the ratio is more like 15 to 1.

Still, says Scofield, when he opened his lab at OMRF in the early 1990s, few scientists seemed interested in digging deeper into these sex disparities. A prevailing theory was that higher levels of hormones, especially during childbearing years, made women more prone to autoimmune diseases. Yet, says Scofield, “It was just considered an interesting question that wasn’t really studied.”

Women typically have two X chromosomes, while men usually carry one X and one Y. As the result of what he at first thought was a mix-up of samples, Scofield identified a male lupus patient who had an extra X chromosome, a condition known as Klinefelter’s syndrome. He and other OMRF researchers then decided to run genetic analyses of biological samples they’d gathered from almost 1,000 people with lupus. Only 200 or so were men, but among them, the researchers found five with Klinefelter’s. This led Scofield to a revelation of sorts.

“It turned out that men with Klinefelter’s syndrome had the same risk of lupus as women,” he says. So, at least for this particular autoimmune disease, “The primary risk factor is not whether you’re a man or a woman. It’s how many X chromosomes you have.”

Scofield’s research now centers on trying to tease out how these chromosomal differences set the stage for molecular and genetic changes that spur autoimmune diseases. He’s also curious about the role that sex hormones like estrogen may play. And here, the story ties back to the research of his OMRF colleague Kovats.

“In many ways, the female immune system works better than the male immune system,” Kovats says. Scientists have come to see autoimmunity as an overactive immune system, one that launches a protective volley against some sort of external trigger (perhaps a virus) and then continues that response against its own cells and organs. So, she says, autoimmunity may prove to be a sort of “trade-off,” the biological price that women pay for having a more vigilant immune system.

The long game, say both Kovats and Scofield, is to develop a fuller, more nuanced picture of human disease, one that takes into account the many factors associated with sex. That includes, says Scofield, variables that go beyond biology.

“Think of common diseases like hypertension, lung cancer and pancreatic cancer. All of them are much more common in men,” he says. “Some of that has got to be biologic differences. Some is not.” For example, he says, the sex differences associated with lung cancer have a clear environmental component: Men smoke more.

The goal of research going forward should be to identify as many of those components – behavioral, environmental, genetic, sex-linked – as possible. That way, clinicians can control for them and modulate their courses of treatment accordingly. In some cases, that may mean a specific drug that works better in one sex. In others, it may be a specific type of hormone replacement therapy tailored to a person’s unique biological profile.

The Longevity Paradox

For as long as statistics have been kept, women have outlived men. Part of that is linked to behavior: Men are more likely to die by suicide, in car accidents and as victims of violent crimes. Nevertheless, as people reach their 80s, 90s and beyond, a time when those variables should begin to fade into the statistical background, women’s survival advantage continues to grow.

According to Boston University’s New England Centenarian Study, of Americans who reach the age of 100, 85% are women. And of those who join the hyper-exclusive ranks of supercentenarians, those aged 110 or more, the female prevalence may rise to 90%. Still, the study’s leaders note that while women “far and away win the longevity marathon,” the men who make it to these advanced ages “are generally functionally better off and healthier.”

OMRF’s Stout acknowledges this seeming paradox. “Based on the scientific literature,” he says, “there’s a much higher probability of your child living longer if they’re female. But there’s also a stronger chance of a female having frailty over an age-matched male.”

Increasingly, researchers recognize that sex-specific biological mechanisms are helping drive these outcomes, says Stout. But what, exactly, are those mechanisms? And how much do they contribute relative to other factors?

“Those are things we just don’t know,” he says.

When it comes to sex differences in disease, there remain more questions than answers. But, driven in no small part by funders like the NIH, scientists now are focusing their microscopes on those questions.

At OMRF’s most recent scientific retreat, that research trend was evident.

The annual event brings together OMRF’s research staff for two days. However, due to the pandemic, the retreat went on a three-year hiatus from 2020 through 2022. When the event returned in 2023, a number of the featured presentations focused on sex as a biological variable.

“That was a huge difference,” says Scofield, who’s been attending the event for decades. Indeed, he can’t remember a single presentation by a colleague on the topic at the 2019 retreat. Or, for that matter, at any previous retreat.

Of course, it’s one thing to study a problem, another to find a solution. But you can’t get answers without asking questions. And at OMRF, that’s precisely what researchers are now doing.

Data Nerd

Dr. Courtney Montgomery is taking number-crunching at OMRF to new heights

These days, a single experiment in an OMRF lab can generate enough data to fill more than 75 laptops. To make scientific sense of that much information, researchers need mathematicians, computer scientists and enough hardware and software to power a midsized technology company.

Enter Dr. Courtney Montgomery.

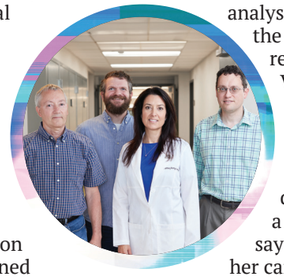
Montgomery first came to OMRF in 1995. After graduating from Oklahoma City University with a degree in biology (despite a two-semester detour as a vocal performance major), the Duncan native was preparing to apply for medical school when she took what she thought would be a temporary job as a research technician in an OMRF lab. The team was studying lupus genetics, and soon, she moved from processing blood samples to data analysis.

"It opened my eyes," Montgomery says. She met a biostatistician, a job she'd never heard of. Biostatisticians apply statistical techniques to research in health-related fields, and Montgomery saw the emerging field as a way to marry her fascination with the human body and her love of mathematics.

Montgomery decided to pursue a joint career path in biostatistics and genetics. While working full-time at OMRF, she earned her master's degree in biostatistics at the University of Oklahoma Health Sciences Center. At the same time, she took short courses in human genetics at a half-dozen other institutions. The field was so young that there were just two formal degree programs in the U.S. As a result, scientists like Montgomery often found themselves creating their own training. "I was cobbling together every bit of information I could," she says.

She earned a Ph.D. in genetic and molecular epidemiology from Ohio's Case Western Reserve University and joined the school's faculty to study lupus and cancer genetics. But when OMRF reached out in 2008, she accepted an offer to move her laboratory home.

Since then, her research has focused on sarcoidosis, a rare and sometimes fatal disease that starts in the immune system and causes inflammation. With experiments that can spit out results equivalent to a spreadsheet with 200 million columns and 3 billion rows, she's also leaned into her biostatistics expertise to develop ways to manage and analyze an ever-growing mountain of biological data.



Led by Dr. Courtney Montgomery, the Center for Biomedical Data Sciences team is helping OMRF researchers untangle vast amounts of data.

A runner and self-described "adrenaline junkie" with a love for extreme sports like obstacle courses, bungee jumping and parasailing, Montgomery says tackling complicated math problems takes her to a "happy place." Thinking about numbers, she says, "is quite calming. It takes all of your focus."

Montgomery's reputation as a "go-to" data-cruncher spread among her OMRF colleagues, who face similar issues. "Researchers are now generating massive amounts of data," says Dr. Bill Freeman, who studies diseases of aging at OMRF. "Dr. Montgomery has the rare skill set that can help make sense of that data and is great at helping other OMRF scientists build these skills to apply to their research."

Over time, OMRF researchers increasingly turned to Montgomery for assistance processing their own data. As the need grew more acute among faculty members, OMRF decided to create a Center for Biomedical Data Sciences, which would add new computing and data analysis capabilities to support the work of all foundation researchers. Montgomery, says Vice President of Research Dr. Courtney Griffin, was an exciting choice to serve as the center's first director.

"She brings outstanding data science credentials and a deep knowledge of OMRF," says Griffin. "She's devoted her career to working with large and complex data sets, and we're excited to see her use these skills to accelerate projects across the whole foundation."

The federal government awarded OMRF funding for construction of the center, which will replace outmoded laboratories built in the 1950s. The project will begin in late 2023. In the meantime, Montgomery is leading a team of data scientists who have already begun to work with numerous OMRF researchers. One of those is Dr. Audrey Cleuren.

Cleuren joined OMRF from the University of Michigan in 2021. She studies how a particular cell type in our blood vessels connects to sepsis and Alzheimer's. Advanced imaging technology can map precisely where hundreds of genes are expressed in an organ, information that helps her untangle how the cells she's interested in function.

However, making sense of the data involves a good deal of untangling, too. That's where Montgomery's data science team comes in. And they are taking an approach that they hope, will provide OMRF's scientists with the tools they need to allow them to help themselves.

"At other institutions, you might hand over your data and tell them what you need, wait, and then you get a bill. Here, they're walking us through it, showing us what they did, and helping us do it ourselves," says Cleuren. "It's very efficient."

Montgomery's group is now working on an artificial intelligence database OMRF scientists will be able to use to find other research related to their results, both internally and externally. The first of these AI tools at OMRF will be devoted to autoimmune disease.

"Making these connections could take a researcher months on their own," says Montgomery. "Our labs will be able to say, 'Here's this thing, tell me what else has been done on this thing.' It's going to fast-track scientific discovery."

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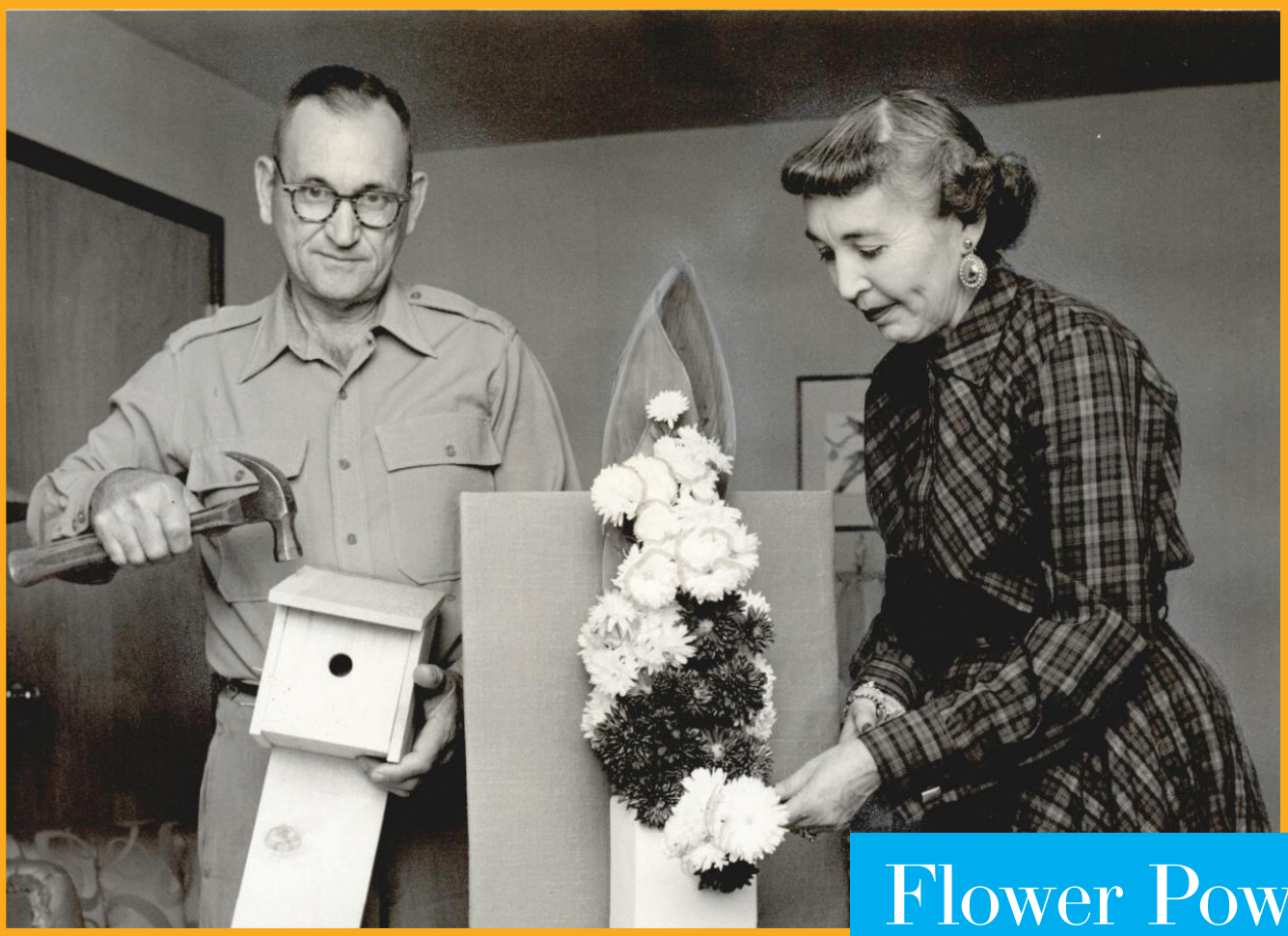

Flower Power

In 1958, members of Oklahoma City's Mr. & Mrs. Garden Flower Club created seasonal arrangements to brighten OMRF's research hospital. The group, co-chaired by Mr. and Mrs. James Taylor, pictured, also created birdhouse kits for patients young and old to assemble.